1.2 D3 refers to myelin protein or fragments in the context of therapy but not diagnosis. It does not refer to neurofilaments. D3 does not deprive claim 8 of novelty. We believe that a claim to a kit comprising either of these agents as test antigen for the specified diseases is justifiable.

2.1 The Examiner refers to D1 and D2. D1 is a scientific literature counterpart to D2 and both come from the same source (the present Applicant). These disclosures are based on the postulate that the bovine disease is caused by infection with Acinetobacter species.

But in neither of D1 and D2 is there any suggestion or hint of the possibility of a much more convenient diagnostic test using the available materials (myelin or neurofilaments) as defined in claim 1. It was not within the foresight of the present inventor to propose the claimed method even though he is the champion of the theory of a molecular mimicry mechanism underlying these diseases.

Furthermore, the Examiner seems to have overlooked the fact that in the first paragraph of page 6 of the application the MAN test is said to consist of separate measurements of myelin and neurofilaments "as well as to specific antibodies" to the Acinetobacter species. The MAN test therefore indicates that the detected myelin and neurofilament antibodies are not the same antibodies as those which are detected as specific to the Acinetobacter organisms. The Examiner's conclusion on this point is therefore not correct.

It is not understood why the Examiner refers to the acinetobacter species at all in the argument against claim 1 and its dependent claims. Testing for these separate antibodies in combination is not introduced until claims 7 and 10 of the application. This is the preferred method and test kit for achieving maximum certainty of diagnosis in the context of the molecular mimicry hypothesis which lies at the root of the present inventor's whole approach to this problem.

Item VII

As pointed out above D1 is the literature paper corresponding to D2 which is mentioned in the present application. In our view, D3 is not of sufficient relevance to justify mention in the present context.

Accordingly, it is not seen necessary to make any significant changes to the claims of the present application, or to amend the description other than as indicated at the start of this response.

Yours faithfully,

Ian Tollett
encs.

International Preliminary Examining Authority
European Patent Office
Erhardtstrasse 27
D-80331 Munich
Germany

Our Ref : IT/SC/N8976

18 October 2000

Dear Sirs,

International Patent Application PCT/GB99/03936

We now respond to the Written Opinion dated 8 August 2000 on the above application.

First, we wish to replace the expression "myelin neurofilaments" throughout this application by the more appropriate term "neurofilaments". As is well known, neurofilaments are contained within a protective myelin sheath, and the original expression was used in this sense. However, it is evident that the expression has caused an apparent misunderstanding, in being taken to mean myelin "fragments" e.g. as in the Examiner's reference to "fragments" of myelin protein in D3.

We therefore file the enclosed revised version of the application with the correct term "neurofilaments" used throughout in place of "myelin neurofilaments". Apart from the consequential change on new page 3 line 17 (removal of "thereof") this is the only change that has been made. Clerical errors on original page 5, lines 6 and 10, and on original page 6 line 11 have also been corrected.

The Examiner will note that the correct term "bovine neurofilaments" has been given in section (1) of the ELISA test described on original page 3 line 24 of the application in relation to Antigen B obtained from Sigma Chemical Co.

A copy of the relevant page of Sigma catalogue entry for their product is enclosed in support of our proposal. This refers to both neurofilaments and antibodies to neurofilaments. Also, on page 5 of the application (line 5 from the foot of the page) the two antigens are correctly referred to and again on page 6 of the application the correct term has been given in relation to the MAN index.

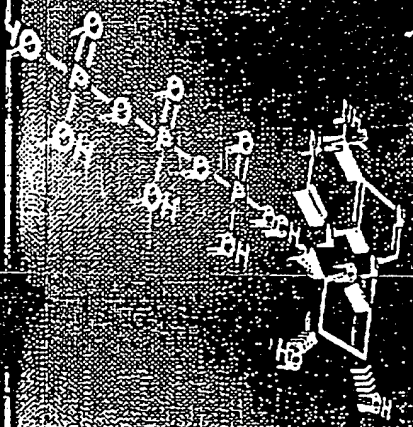
Should the Examiner see any difficulty over this change of terminology we would appreciate the opportunity to discuss the matter by telephone.

Referring now to the relevant numbered paragraphs in the Written Opinion we have the following comments:

2000
2001

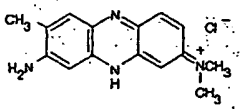
Biochemicals and Reagents

FOR LIFE SCIENCE RESEARCH



SIGMA

PRODUCT NUMBER			£
	(Continuation of) **NEURAMINIDASE**		
N 5631 [-0°C]	**Type VIII: Chromatographically purified From Clostridium perfringens Prepared from Type V** Dialyzed and lyophilized powder containing approx. 90% protein (Biuret) **Activity:** 10-20 units per mg protein (NAN-lactose) and approx. 4 units per mg protein (mucin). May contain protease and NAN-aldolase. *[9001-67-6]*	1 unit 5 units 10 units 50 units	37.10 122.00 200.40 715.20
N 2133 [-0°C]	**Type X: From Clostridium perfringens** A further purification by affinity chromatography of our Type VIII (N 5631). **Dialyzed and lyophilized powder containing approx. 85% protein (Bradford). Activity:** 150-400 units per mg protein (NAN-lactose). *[9001-67-6]*	1 unit 5 units 10 units 50 units	43.90 145.30 238.70 852.20
N 6021 [-0°C]	**Type II-A: Insoluble enzyme attached to beaded agarose. From Vibrio cholerae** Lyophilized powder stabilized with lactose. **Activity:** 45-135 units per g of agarose (NAN-lactose). One ml of gel will yield 1.5-4.5 units. Prepared from Neuraminidase, Type II. R: 20-42/43-36/37/38 S: 26-36-22	1 unit 5 units	81.10 320.00
N 5254 [2-8°C]	**Type VI-A: Insoluble enzyme attached to beaded agarose. From Clostridium perfringens** Suspension in 2.0 M $(NH_4)_2SO_4$ solution, pH 7.0. **Activity:** 0.6-1.8 units per ml of gel (NAN-lactose). One gram of agarose will yield 20-60 units. Prepared from Neuraminidase, Type VI.	1 unit 10 units	48.80 289.10
N 4883 [2-8°C]	**Type X-A: Insoluble enzyme attached to beaded agarose. From Clostridium perfringens** Suspension in 2.0 M $(NH_4)_2SO_4$ solution, pH 7.0. **Activity:** 20-30 units per gram of agarose (NAN-lactose). One ml gel will yield 0.6-1.0 unit. Prepared from Neuraminidase, Type X.	1 unit 5 units	99.20 326.60
	NEURAMINIDASE, Positionally Specific **Recombinant; expressed in E. coli** **Solution in 20 mM Tris-HCl, pH 7.5, 25 mM NaCl** **Unit Definition:** One unit will hydrolyze 1 µmole of 4-methylumbelliferyl α-D-N-acetylneuraminide per min at pH 5.0 at 37°C. **Absence of contaminants:** enzymes are expressed in glycosidase-free hosts; contaminating β-galactosidase, α-mannosidase, β-hexosaminidase, α-fucosidase, and proteases are not detectable. Provided with 5× reaction buffer (250 mM sodium phosphate, pH 6.0). *[9001-67-6]*		
N 7271 [2-8°C]	**α-2→3-Neuraminidase** Releases α-2→3-linked N-acetylneuraminic acid from complex oligosaccharides.	0.2 unit	171.20
N 5521 [2-8°C]	**α-2→(3,6)-Neuraminidase** Releases α-2→3- and α-2→6-linked N-acetylneuraminic acid from complex oligosaccharides.	0.4 unit	171.20
N 8271 [2-8°C]	**α-2→(3,6,8,9)-Neuraminidase** Releases α-2→3-, α-2→6-, α-2→8, and α-2→9-linked N-acetylneuraminic acid from complex oligosaccharides.	0.2 unit	171.20
	NEURAMIN-LACTOSE *See:* N-Acetylneuramin-lactose *Page 41*		

PRODUCT NUMBER			£
	NEUROACTIVE COMPOUNDS, NEUROCHEMICALS, AND RELATED COMPOUNDS *See:* Neurochemicals Section *Page 1636*		
	NEUROFILAMENT, ANTIBODIES TO *See:* Immunochemicals *Page 1130*		
	NEUROFILAMENTS	Protein	
N 1022 [-20°C]	**From Bovine Spinal Cord** **Lyophilized from a solution containing 6 M urea, 10 mM sodium phosphate, 5 mM EDTA and 1% β-mercaptoethanol, pH 7.5.** Intermediate filaments found in axons of large myelinated fibers, most neurons, astrocytes and Schwann cells Prepared using a modification of Dahl, D., et al., Anal. Biochem., **126**, 165 (1982).	500 µg	349.50
	NEUROGRANIN FRAGMENT 28-43 *See:* Bioactive Peptides *Page 1069*		
	NEUROKININS *See:* Bioactive Peptides *Page 1098*		
	NEUROMEDINS *See:* Bioactive Peptides *Page 1098*		
	NEUROPEPTIDE K *See:* Bioactive Peptides *Page 1054*		
	NEUROPEPTIDE Y *See:* Bioactive Peptides *Page 1054*		
	NEUROPHYSIN I	100 µg	120.10
N 2404 [2-8°C]	**From Bovine Pituitaries** A protein found in vasopressin- and oxitocin-containing neurons in the hypothalamus that is associated with the transport of these hormones to the posterior pituitary *[63231-59-4]*		
	NEUROTENSIN and RELATED PEPTIDES *See:* Bioactive Peptides *Page 1061*		
	NEUROTOXINS *See:* Toxins, Snake *Page 964*		
	NEUROTOXINS, Kits of *See:* Venoms *Page 1011*		
	NEUROTRANSMITTERS, NEUROPEPTIDES, NEURONAL ENZYMES AND HORMONES, ANTIBODIES TO *See:* Immunochemicals *Page 1196*		
	NEUTRALIZED CHARCOAL *See:* Charcoal, Activated *Page 231*		
	NEUTRAL RED (C.I. 50040; 3-Amino-7-dimethylamino-2-methylphenazine hydrochloride) **pH range 6.8 (red) - 8.0 (yellow).** Useful as an indicator for preparing neutral red paper, and as a biological stain.  *[553-24-2]* $C_{15}H_{16}N_4 \cdot HCl$ FW 288.8		
N 7005 [2-8°C]	**Purified Dye Content: >90%** *See also:* Tissue Culture Media and Reagents *Page 1762*	1 g 5 g 25 g	13.80 40.70 132.60
N 8906 [2-8°C]	**Dye Content: ≥80%**	1 g 5 g 25 g	10.20 33.90 112.90
N 2880 [RT]	**Practical Grade** **Dye Content: Approx. 60%**	25 g 100 g	22.40 65.40

(Continued)